PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/48, 9/28

A1

(11) International Publication Number: WO 94/25009

(43) International Publication Date: 10 November 1994 (10.11.94)

(21) International Application Number: PCT/US94/04089

(22) International Filing Date: 13 April 1994 (13.04.94)

(30) Priority Data:
08/056,701 30 April 1993 (30.04.93) US

(71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventors: RUSSEL, Carmelita, Macklin; 607 Vincennes Court, Cincinnati, OH 45231 (US). DINES, Allen, L.; 7509 Muchmore Close, Cincinnati, OH 45243 (US). UPSON, James, Grigg; 11268 Springfield Pike, Springdale, OH 45246 (US).

(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).

(81) Designated States: CA, CN, FI, JP, NO, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: COATED PHARMACEUTICAL COMPOSITIONS

(57) Abstract

Pharmaceutical composition suitable for coating comprising a composition for oral administration in unit dosage form wherein said composition has been coated with from about 0.01 % to about 10 % by weight of the composition with a volatile aromatic compound selected from the group consisting of 3-1-menthoxy propano-1,2-diol, N-substituted-p-menthano-3-carboxamides and acyclic carboxamides and mixtures thereof.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

COATED PHARMACEUTICAL COMPOSITIONS

TECHNICAL FIELD

The present invention relates to pharmaceutical compositions for oral administration coated with one or more volatile aromatics selected from the group consisting of 3-l-menthoxy propane-1,2-diol, N-substituted-p-menthane-3-carboxamides and acyclic carboxamides and mixtures thereof.

BACKGROUND OF THE INVENTION

The common cold, although not usually a serious illness, is a highly prevalent, discomforting and annoying infliction. The term "common cold" is applied to minor respiratory illnesses caused by a variety of different respiratory viruses. While rhinoviruses are the major known cause of common colds, accounting for approximately 30 percent of colds in adults, viruses in several other groups are also important. While immune responses occur, and infection with some respiratory tract viruses therefore could be prevented by a vaccine, development of a polytypic vaccine to cover all possible agents is impractical. Thus, the problem of controlling acute upper respiratory disease presents complex challenges, and the long-desired discovery of a single cure for the common cold is an unrealistic expectation.

Typical symptoms of the common cold are mild malaise, sore throat and nasal complaints. Nasal discharge, nasal congestion and/or sneezing frequently are present. Also common are sore, dry or scratchy throat and hoarseness and cough. Other symptoms may include mild burning of the eyes, loss of smell and taste, a feeling of pressure or fullness in the sinuses or ears, headache, and vocal impairment. Flu symptoms are similar but usually of greater severity, including fever, generalized aches and pains, fatigue and weakness, and chest discomfort. Allergy symptoms are more akin to the common cold, with more frequent/severe sinus pressure, drainage and headaches.

Pharmaceutical compositions safe and effective for treating colds, flu, and allergies are well known. Over-the-counter medications provide symptomatic relief of such illnesses. At present, only symptomatic treatment is available for the common cold; the majority of these drugs are taken orally. Exemplary prior art oral compositions for treatment of nasal and other cold, flu, allergy and sinus

symptoms and the discomfort, pain, fever and general malaise associated therewith generally contain an analgesic (aspirin or acetaminophen) and one or more antihistamines, decongestants, cough suppressants, antitussives and expectorants. Other specific pharmaceutical actives for nasal symptoms (e.g., congestion) generally contain either oxymetazoline or phenylephrine. These actives are generally delivered topically to the nasal mucosa via a nasal spray. For individuals with certain medical conditions such as heart disease, hypertension, diabetes or thyroid disorders, oral drugs such as decongestants could pose a risk of unfavorable drug interactions and may cause an adverse reaction. It would, therefore, be highly desirable to deliver relief from specific nasal symptoms via compositions without the need for such pharmaceutical actives.

Nasal delivery of therapeutic agents has been well known for a number of years. See, for example, U.S. Patent 4,749,700 to Wenig, issued June 7, 1988, U.S. Patent 4,778,810 to Wenig, et al., issued October 18, 1988 and U.S. Patent 4,729,997 to Wenig issued March 8, 1988. Menthol has been administered orally from lozenges and the like as well as delivered to the nasal mucosa from an inhaler containing a wick and no other excipients, see, for example, Clinical Otolaryngology, 1988, vol. 13, pps. 25-29.

Coated pharmaceutical compositions have also been used to provide improved aesthetics, taste- and/or odor-masking and to provide flavoring and fragrances to tablets and the like, see, for example, U.S. Patent 5,089,715 to McCabe et al., issued March 24, 1992.

It has been discovered that oral pharmaceutical compositions coated with one or more of a volatile aromatic compound selected from the group consisting of 3-l-menthoxy propane-1,2-diol, N-substituted-p-menthane-3-carboxamides and acyclic carboxamides thereof provide the user with improved actual and/or perceived relief from nasal symptoms such as congestion and the like as well as sore throat and the like. In addition, such compositions will not cause drowsiness or other side effects attendant with oral decongestants.

Prior art formulations for treating cough, cold, cold-like, allergy and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith typically contain one or more of the pharmaceutical actives which are analgesics, anesthetics, antihis-

tamines, decongestants, cough suppressants, antitussives and expectorants.

It is an object of the present invention to provide compositions and methods useful for treating cough, cold, cold-like, allergy and flu symptoms in humans and lower animals in need of such treatment. Another object is to provide such compositions and methods having improved actual and/or perceived benefits, e.g., speed of relief and/or duration of relief, and/or improved aesthetics.

These and other objects of the present invention will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention is directed to pharmaceutical compositions suitable for coating comprising a composition for oral administration in unit dosage form wherein said composition has been coated with from about 0.01% to about 10% by weight of the composition with a volatile aromatic compound selected from the group consisting of 3-l-menthoxy propane-1,2-diol, N-substituted-p-menthane-3-carboxamides and acyclic carboxamides and mixtures thereof.

The present invention is also directed to methods for treating cough, cold, cold-like, allergy, and flu symptoms in a human or lower animal, said method comprising administering these compositions to a human or lower animal in need of such treatment.

All percentages and ratios used herein are by weight, and all measurements are made at 25°C, unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions suitable for coating comprising a composition for oral administration in unit dosage form wherein said composition has been coated with from about 0.01% to about 10% by weight of the composition with a volatile aromatic compound selected from the group consisting of 3-l-menthoxy propane-1,2-diol, N-substituted-p-menthane-3-carboxamides and acyclic carboxamides and mixtures thereof.

The components of the compositions according to the present invention, and representative amounts, as well as the present invention methods are described in detail as follows.

Volatile Aromatics:

The pharmaceutical compositions of the present invention are coated with a coating comprising a volatile aromatic selected from the group consisting of 3-l-menthoxy propane-1,2-diol, N-substituted-p-

menthane-3-carboxamides and acyclic carboxamides and mixtures thereof. While not to be limited by theory, it is believed that the benefits obtained by the use of these coolants in the compositions of the present invention are the result of the unique cooling profiles for these compounds.

3-l-menthoxy propane 1,2-diol is fully described in detail in U.S. Patent 4,459,425, issued July 10, 1984 to Amano et. al, incorporated herein by reference in its entirety. This volatile aromatic is commercially available, being sold by Takasago Perfumery Co., Ltd., Tokyo, Japan.

The N-substituted-p-menthane-3-carboxamides are fully described in U.S. Patent 4,136,163 to Watson et al., issued January 23, 1979 incorporated herein by reference in its entirety. The most preferred volatile aromatic of this class is N-ethyl-p-menthane-3-carboxamide which is commercially available as WS-3 from Wilkinson Sword Limited.

Useful acyclic carboxamides are fully described in U.S. Patent 4,230,688 to Rowsell et al., issued October 28 1980 incorporated herein by reference in its entirety. The most preferred volatile aromatic of this class is N,2,3-trimethyl-2-isopropylbutanamide which is commercially available as WS-23 from Wilkinson Sword Limited.

Preferred for use herein is a mixture of 3-l-menthoxy propane 1,2-diol and N-ethyl-p-menthane-3-carboxamide in a ratio of about 3:1. The most preferred coating comprises a mixture of 3-l-menthoxy propane 1,2-diol, N-ethyl-p-menthane-3-carboxamide and N,2,3-trimethyl-2-isopropylbutanamide in a ratio of 2:1:1, respectively.

These volatile aromatic compounds are present at a level of from about 0.001% to about 10%, preferably at from about 0.001% to about 5%, more preferably from about 0.001% to about 0.5% by weight of the pharmaceutical compositions of the present invention. These volatile aromatic materials can be applied directly to the compositions of the present invention, or incorporated into a pharmaceutically-acceptable coating as described below.

Pharmaceutically-Acceptable Dosage Form:

Various oral dosage forms suitable for coating can be used, including such solid forms as tablets, capsules, pills and lozenges. These oral forms can contain a safe and effective amount of a pharmaceutical active component. Solid oral dosage forms preferably comprise from about 0.1% to about 99%, more preferably from about 25% to

about 99%, and most preferably from about 50% to about 99% of a pharmaceutical active component.

These dosage forms contain compatible solid or liquid filler diluents or encapsulating substances which are suitable for oral administration to a human or lower animal. The term "compatible", as used herein, means that the components of the compositions of the present invention are capable of being commingled with the pharmaceutical active, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the compositions under ordinary use situations. Pharmaceutically-acceptable carrier materials must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human being treated. Preferably the present invention compositions comprise from about 0.1% to about 99.99% of one or more pharmaceutically-acceptable carrier materials.

Tablets can be compressed, molded, triturated, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents.

Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553-1593 (1980), incorporated herein by reference. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in U.S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein.

Also useful are soft and hard gelatin capsules wherein the shell is either coated, or alternatively, the volatile aromatic compound is contained within the shell material. Preferably, the gelatin shell is essentially transparent so as to enhance the aesthetic qualities of the capsule. Soft and hard gelatin shells generally comprise gelatin, a plasticizer and water. The starting gelatin material generally used in the manufacture of these capsules is obtained by the partial hydrolysis of collagenous material. Gelatin suitable for capsule manufacture is commercially available from the Sigma Chemical Company,

St. Louis, Mo. For a general description of gelatin and gelatin-based capsules, see Remington's Pharmaceutical Sciences, 16th ed., Mack Publishing Company, Easton, Pa. (1980), page 1245 and pages 1576-1582; and U.S. Patent 4,935,243, to Borkan et al., issued June 19, 1990; these two references being incorporated herein by reference in their entirety.

One or more plasticizers is incorporated to produce a gelatin shell. Useful plasticizers of the present invention include glycerin, sorbitan, sorbitol, or similar low molecular weight polyols, and mixtures thereof.

The gelatin shells of the instant invention can be prepared by combining appropriate amounts of gelatin, water, plasticizer, and any optional components in a suitable vessel and agitating and/or stirring while heating to about 65°C until a uniform solution is obtained. Hard gel capsules can then be used for encapuslating the desired quantity of fill material employing methods known to the skilled artisan. Soft gelatin shell compositions containing the desired quantity of the fill composition are made by employing standard encapsulation methodology to produce one-piece, hermetically sealed, soft gelatin capsules.

The gelatin capsules are formed into the desired shape and size so that they can be readily swallowed. The gelatin capsules of the instant invention are of a suitable size for easy swallowing and typically contain from about 100 mg to about 2000 mg of the pharmaceutical active composition. The coolant can be added either as a seperate coating applied directly to the gelatin capsule, or it can be incorporated into the gelatin capsule shell itself without the need for a seperate coating step. Gelatin capsules and encapsulation methods are described in P.K. Wilkinson et al., "Softgels: Manufacturing Considerations", Drugs and the Pharmaceutical Sciences, 41 (Specialized Drug Delivery Systems), P. Tyle, Ed. (Marcel Dekker, Inc., New York, 1990) pp.409-449; F.S. Hom et al., "Capsules, Soft", Encyclopedia of Pharmaceutical Technology, vol. 2, J. Swarbrick and J.C. Boylan, eds. (Marcel Dekker, Inc., New York, 1990) pp. 269-284; M.S. Patel et al., "Advances in Softgel Formulation Technology", Manufacturing Chemist, vol. 60, no. 7, pp. 26-28 (July 1989); M.S. Patel et al., "Softgel Technology", Manufacturing Chemist, vol. 60, no. 8, pp. 47-49 (August 1989); R.F. Jimerson, "Softgel (Soft Gelatin Capsule) Update", Drug Development and Industrial Pharmacy (Interphex '86

Conference), vol. 12, no. 8 & 9, pp. 1133-1144 (1986); and W.R. Ebert, "Soft Elastic Gelatin Capsules: A Unique Dosage Form", Pharmaceutical Technology, vol. 1, no. 5, pp. 44-50 (1977); these references are incorporated by reference herein in their entirety.

Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents, colorants and the like to provide a palatable and pleasant looking final product, antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or propyl paraben, potassium sorbate, or sodium benzoate, to prolong and enhance shelf life. A preferred optional component is also caffeine.

Pharmaceutical Actives:

The pharmaceutical compositions according to the present invention optionally comprise a safe and effective amount of a pharmaceutical active, preferably a pharmaceutical colds actives useful for treating cough, cold, cold-like, allergy and/or flu symptoms. Such pharmaceutical actives are well known, and are generally recognized as being an active having analgesic, anti-inflammatory, anesthetic, antihistamine, decongestant, cough suppressant, demulcents, antitussive, and/or expectorant properties.

The phrase "safe and effective amount", as used herein, means an amount of a compound or composition high enough when administered orally to significantly positively modify the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of the pharmaceutical active will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific pharmaceutical active employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician. Typically, the pharmaceutical active(s) comprise from about 0.001% to about 99.9%, by weight, of the pharmaceutical compositions of the present invention, preferably from about 0.001% to about 75%, and most preferably from about 0.01% to about 30%.

Examples of actives commonly utilized in cough/cold preparations are, for example, a decongestant such as pseudoephedrine, phenyl-

propanolamine, phenylephrine and ephedrine, their pharmaceutically acceptable salts; an antitussive such as dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, menthol, hydrocodone, hydromorphone, fominoben, their pharmaceutically-acceptable salts; an expectorant or mucolytic such as glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and bromhexine, ambroxol, their pharmaceutically acceptable salts; and an antihistamine such as chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbromphreniramine, triprolidine, azatadine, doxylamine, tripelennamine, cyproheptadine, hydroxyzine, clemastine, carbinoxamine, phenindamine, bromodiphenhydramine, pyrilamine, their pharmaceutically acceptable salts, as well as the non-sedating antihistamines which include acrivastine, AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, and terfenadine, their pharmaceutically acceptable salts: all of these components, as well as their acceptable dosage ranges are described in the following: U.S. Patent 4,783,465 to Sunshine et al., issued November 8, 1988, U.S. Patent 4,619,934 to Sunshine et al., issued October 28, 1986, which are incorporated by reference herein. Also useful are bronchodilators such as terbutaline, atropine, aminophylline, epinephrine, isoprenaline, metaproterenol, bitoterol, theophylline and albuterol. Also used are analgesic compounds such as aspirin, acetaminophen, ibuprofen, and naproxen; and topical anesthetics/analgesics such as phenol, benzocaine, hexyl resorcinol, and dyclonine.

Other preferred pharmaceutical actives include ingestible pharmaceutical agents effective for treating the gastrointestinal tract (e.g., symptoms such as heartburn, stomachache and indigestion), such as bismuth-containing agents and H_2 receptor-blocking anti-secretory agents. Preferred antacid agents have stomach acid neutralizing capacities, such as those agents selected from the group consisting of: aluminum carbonate, aluminum hydroxide, aluminum phosphate, aluminum hydroxy-carbonate, dihydroxy aluminum sodium carbonate, aluminum magnesium glycinate, dihydroxy aluminum amino acetate, dihydroxy aluminum aminoacetic acid, calcium carbonate, calcium phosphate, aluminum magnesium hydrated sulfates, magnesium aluminate, magnesium alumino silicates, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate,

sucralfate, and mixtures thereof. Bismuth-containing agents include, for example, bismuth subsalicylate, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subcarbonate, bismuth subgalate, and mixtures thereof. A particularly preferred bismuth salt is bismuth subsalicylate. Examples of H_2 receptor-blocking anti-secretory agents include ranitidine and cimetidine. Preferred antacid agents for use herein are aluminum hydroxide, magnesium hydroxide, dihydroxy aluminum sodium carbonate, calcium carbonate, and mixtures thereof. Most preferred is calcium carbonate.

Other pharmaceutical actives useful in the present invention calcium channel blockers, beta-blockers, antibacterials, antidepressants, antidiabetics, anti-emetics, cerebral stimulants, sedatives, anti-parasitics, diuretics, muscle relaxants, anti-Parkinsonian agents, bronchodilators, cardiotonics, antibiotics, antivirals, nutritional supplements (such as vitamins, minerals, fatty acids, amino acids, and the like), and mixtures thereof.

For solid dosage forms, the volatile aromatic coolants of the present invention are applied directly to the surface of the dosage form alone, or preferably by being incorporated into any conventional pharmaceutically-acceptable coating. Suitable coating techniques are described in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa. (1985), pages 1233-43, this reference being incorporated herein by reference. The preferred film coating of this invention is comprised of a commercial film-coating product designed for aqueous film coating containing a water-soluble, film-forming resin, hydroxypropyl methylcellulose and polyethylene glycol (or other suitable plasticizing agents such as propylene glycol or glycerin) and optionally containing titanium dioxide (or other colorant or opacifying agent). Such a product is commercially available under the trade name Opadry White™ (Colorcon, West Point, Pa.). A suitable blend comprises 0 to about 20% w/w titanium dioxide or colorant, about 5 to about 95% w/w hydroxypropyl methylcellulose, and 0 to about 25% w/w polyethylene glycol. The most preferred embodiment comprises 10.5% non-water additives, of which 7.5% is Opadry. Therefore, most of the weight of the non-water additives of the coating dispersion is comprised of Opadry. More than 25% Opadry makes the coating too thick to spray easily while concentrations that are too low decrease the efficiency of coating. This blend plus flavoring and sweetening agents is added to purified water at ambient temperature in

a vortex mixer such as a Lightnin Mixer Model V-7 (Mixing Equipment Co., Rochester, N.Y.). Other Opadry coating products such as Opadry Clear or Opadry with various pigment lakes may also be used in the invention to change the appearance of the tablets without adversely affecting the flavor characteristics of the invention. Other aqueous film-forming polymers may also be employed in place of hydroxypropyl methylcellulose.

Method of Treatment:

The present invention also relates to a method for treating cough, cold, cold-like, allergy and flu symptoms in a human or lower animal. Said method comprises administering to a human or lower animal in need of such treatment the compositions of the present invention.

The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are given solely for the purpose of illustration and are not to be construed as a limitation of the present invention as many variations thereof are possible without departing from the spirit and scope.

EXAMPLE I

A coated tablet composition for oral administration is prepared by combining the following ingredients:

Tablet:

Ingredients	mg
Acetaminophen	500.0
Pseudoephedrine	30.0
Povidone	37.5
Lactose	102.9
Alcohol	qs*
Stearic Acid	15.0
Talc	22.5
Corn Starch	71.2

* Not part of the final tablet or caplet

Coating

3-l-menthoxy propane-1,2-diol	1.5
Alcohol	4.0
Hydroxypropyl Methylcellulose	8.5
Water	86.0

The acetaminophen, povidone and lactose are blended together. The alcohol is added slowly and mixed well. The wet mass is screened

through a #4 mesh screen. The granulation is dried at 50°C overnight and then sized through a #20 mesh screen. The remaining ingredients are bolted through a #60 mesh screen. The two granulations are mixed and then compressed into tablets using conventional tableting equipment known to those skilled in the art. The tablets are then pan coated with the coating mixture using conventional coating equipment.

Administration of 1 or 2 of the above tablets to a human in need of treatment provides improved relief from cough, cold-like, flu and flu-like symptoms.

EXAMPLE II

A coated hard gelatin capsule composition for oral administration is prepared by combining the following ingredients:

Capsule:

Ingredients	Amount
Ibuprofen	100 mg
Pseudoephedrine HCl	30 mg
Astemizole	5 mg
Glyceryl guaiacolate	100 mg

Coating:

3-l-menthoxy propane-1,2-diol	0.750
N-ethyl-p-menthane-3-carboxamide	0.375
N, 2,3-trimethyl-2-isopropylbutanamide	0.375
Hydroxypropyl Methylcellulose	8.500
Alcohol	4.000
Water	86.000

Triturate active ingredients and q.s. with lactose to selected capsule size. The capsules are then coated with the coolant mixture as described above in Example I.

Administration of 1 or 2 of the above capsules to a human in need of treatment provides improved relief from cough, cold-like, flu and flu-like symptoms.

EXAMPLE III

A soft gelatin capsule for oral administration is prepared by combining the following ingredients:

Solubilized Fill:

Ingredient	W/W%
Polyvinylpyrrolidone 12pf[1]	150.00
Polyethylene Glycol 600	200.00
Ibuprofen	200.00

Pseudoephedrine HCl	30.00
Water	40.00
Ammonium hydroxide 30%	3.00

[1]Available as Kollidon[R] 12pf, from BASF, Parsippany, NJ, 07054.

Soft Gelatin Coating:

Ingredients	W/W%
Gelatin	47.00
Glycerin	15.00
Water	Q.S.
3-l-menthoxy propane-1,2-diol	1.5

The fill ingredients are combined in a suitable vessel and heated with mixing at about 65°C to form a uniform solution. The soft gelatin ingredients are combined and heated to about 65°C to form a uniform mixture. Using standard encapsulation methodology, the resulting solution is used to prepare soft gelatin capsules containing approximately 623 mg of the fill material wherein the volatile aromatic is incorporated into the soft gelatin capsule shell. The resulting soft gelatin capsules are suitable for oral administration.

What is claimed is:

1. An oral pharmaceutical composition comprising a composition suitable for coating in unit dosage form wherein said composition has been coated with from 0.01% to 10% by weight of the composition with a volatile aromatic compound selected from the group consisting of 3-l-menthoxy propane-1,2-diol, N-substituted-p-menthane-3-carboxamides and acyclic carboxamides and mixtures thereof.

2. The composition of Claim 1 wherein said composition comprises a mixture of 3-l-menthoxy propane-1,2-diol and N-ethyl-p-menthane-3-carboxamide, preferably in a weight ratio of 3:1, respectfully.

3. The composition of Claim 1 wherein said composition comprises a mixture of 3-l-menthoxy propane-1,2-diol, N-ethyl-p-menthane-3-carboxamide and N, 2,3-trimethyl-2-isopropylbutanamide preferably in a weight ratio of 2:1:1, respectively.

4. The pharmaceutical composition of Claim 1 which further comprises a pharmaceutical active.

5. The pharmaceutical composition of Claim 4 wherein said pharmaceutical active is a colds active selected from the group consisting of analgesics, anti-inflammatories, anesthetics, antihistamines, decongestants, cough suppressants, demulcents, antitussives, expectorants, and mixtures thereof.

6. The pharmaceutical composition according to Claim 5 wherein the pharmaceutical active is selected from the group consisting of pseudoephedrine, phenylpropanolamine, phenylephrine, ephedrine, dextromethorphan, chlophedianol, carbetapentane, caramiphen, noscapine, diphenhydramine, codeine, menthol, hydrocodone, hydromorphone, fominoben, glyceryl guaiacolate, terpin hydrate, ammonium chloride, N-acetylcysteine and bromhexine, ambroxol, chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, azatadine, doxylamine, tripelennamine, cyproheptadine, hydroxyzine, clemastine, carbinoxamine, phenindamine, bromodiphenhydramine, pyrilamine, acrivastine, AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide,

loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine, terfenadine, terbutaline, atropine, aminophylline, epinephrine, isoprenaline, metaproterenol, bitoterol, theophylline, albuterol, aspirin, acetaminophen, ibuprofen, naproxen, phenol, benzocaine, hexyl resorcinol, dyclonine, the pharmaceutically acceptable salts thereof, and mixtures thereof.

7. A pharmaceutical composition according to Claim 4 wherein the composition is in a dosage form selected from the group consisting of tablets, capsules, pills and lozenges.

8. A pharmaceutical composition according to Claim 7 wherein the composition is in the form of a capsule selected from the group consisting hard gelatin capsules and soft gelatin capsules.

9. A pharmaceutical composition according to Claim 8 wherein the composition is a soft gelatin capsule.

10. An oral pharmaceutical composition comprising a soft gelatin capsule shell wherein said shell comprises from 0.01% to 10% by weight of the composition with a volatile aromatic compound selected from the group consisting of 3-l-menthoxy propane-1,2-diol, N-substituted-p-menthane-3-carboxamides and acyclic carboxamides and mixtures thereof.

11. The pharmaceutical composition of Claim 10 which further comprises a pharmaceutical active.

12. The pharmaceutical composition of Claim 11 wherein said pharmaceutical active is a colds active is selected from the group consisting of analgesics, anti-inflammatories, anesthetics, antihistamines, decongestants, cough suppressants, demulcents, antitussives, expectorants, and mixtures thereof.

13. A method for treating cough, cold, cold-like, allergy, and flu symptoms in a human or lower animal, said method comprising administering to a human or lower animal in need of such treatment the composition of Claim 1.

14. A method for treating cough, cold, cold-like, allergy, and flu symptoms in a human or lower animal, said method comprising administering to a human or lower animal in need of such treatment the composition of Claim 2.

15. A method for treating cough, cold, cold-like, allergy, and flu symptoms in a

human or lower animal, said method comprising administering to a human or lower animal in need of such treatment the composition of Claim 5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/04089

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/48 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR,A,2 127 010 (WILKINSON SWORD LIMITED) 13 October 1972 see page 1, line 4 see page 3, line 38 - page 6, line 8 see page 7, line 1 - line 5 see page 7, line 20 - line 23 see page 8, line 13 - line 17 see page 11, line 3 - line 19 see page 21; example 35	1-17
A	WO,A,92 17164 (THE PROCTER & GAMBLE COMPANY) 15 October 1992 see claims 1-12 see page 5, line 16 - line 24 see page 6, line 1 - line 11	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 July 1994	29.07.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04089

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 15-17 are directed to a method of treatment of the human and animal body the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US 94/04089

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-2127010	13-10-72	AT-B-	335069	25-02-77
		AU-B-	457073	23-12-74
		AU-A-	3860572	09-08-73
		AU-B-	450078	07-06-74
		AU-A-	3860672	09-08-73
		BE-A-	778950	04-08-72
		BE-A-	778951	04-08-72
		CA-A-	968141	27-05-75
		CA-A-	1019551	25-10-77
		CH-A-	549952	14-06-74
		CH-A-	554648	15-10-74
		DE-A,B,C	2202535	17-08-72
		DE-A-	2203947	17-08-72
		FR-A,B	2127011	13-10-72
		GB-A-	1353381	15-05-74
		LU-A-	64713	30-06-72
		NL-A-	7201522	08-08-72
		NL-A-	7201524	08-08-72
		SE-B-	402404	03-07-78
		US-A-	4193936	18-03-80
		US-A-	4178459	11-12-79
		US-A-	4226988	07-10-80
		US-A-	4136163	23-01-79
		US-A-	4150052	17-04-79
		US-A-	4190643	26-02-80
WO-A-9217164	15-10-92	AU-A-	1761492	02-11-92
		EP-A-	0578768	19-01-94
		US-A-	5244670	14-09-93